REMARKS

Claims 1-8 are rejected. Claim 1 has been amended. Claims 1-8 are presently pending in the application. Favorable reconsideration of the application in view of the following remarks is respectfully requested.

The basis for the amendment of claim 1 is found in claim 1 as originally filed, as well as pg. 5, lines 20-31 and pg. 9, lines 12-17 and Fig. 2 of the specification as originally filed.

Rejection of Claims 1-8 under 35 USC § 112:

The Examiner has rejected Claims 1-8 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, since "passing said hybridized DNA complex in a random coil state from a reservoir in a microfluidic device through a narrow channel to cause an acceleration of flow through said channel", is unclear regarding acceleration of the DNA complex and/or the fluid flowing through the channel, regarding the process which actually causes the "acceleration of flow" through the narrow channel, regarding the nature of the acceleration over time, and regarding what causes the hybridized DNA complex to extend into a substantially linear configuration. The Applicants have provided a copy of an article and a slide show as Attachments B-1 and B-2. These documents clarify the nature of the flow and also indicate that one of ordinary skill in the art would understand the terminology, relationships and fluid mechanics as stated in the claims. Pg. 9, lines 1-3 and pg. 11, lines 21-25 of the specification as originally filed indicate that the elongation is temporary.

Rejection of Claims 1-6 Under 35 U.S.C. §102(b):

The Examiner has rejected Claims 1-6 under 35 U.S.C. §102(b) as being anticipated by Bensimon et al (U.S. Patent 6,054,327). The Examiner indicates that several aspects of instant claim 1.c have been broadly interpreted by the examiner, such as passing the hybridized DNA complex "from a reservoir in a microfluidic device", which has been interpreted as moving any portion of the hybridized DNA complex initially in a holding area in a device designed to contain small amounts of liquids, passing the hybridized DNA complex through a "narrow channel to cause an acceleration of flow through said channel" has been interpreted as moving any portion of the hybridized DNA complex through a small passageway, which involves an acceleration of flow through the

passageway. The Examiner therefore states that Bensimon teaches a method of analyzing DNA comprising hybridizing the DNA in solution with probes having fluorescent reagents and then detecting the position of the probes after aligning the DNA, Bensimon also teaches that DNA molecules placed in a channel between cover slips can be aligned by the evaporation flow parallel to a moving meniscus in the channel, DNA molecules in a random coil state fixed at a location in a channel between cover slips is interpreted as the embodiment of the hybridized DNA complex initially being in a "reservoir in a microfluidic device" as recited in instant claim 1.c, as the meniscus initially moves through the channel between the cover slips, there will be an acceleration of fluid flow in the channel and a portion of the DNA complex will pass through the channel as it extends to a linear configuration, which is interpreted as the embodiment of passing the hybridized DNA complex through a "narrow channel to cause an acceleration of flow through said channel, thereby causing said hybridized DNA complex to extend into a substantially linear configuration;" (recited in instant claim 1.c), Bensimon teaches that the probes used to hybridize to DNA can be oligonucleotides, RNA, DNA, and peptide nucleic acids, Bensimon also teaches that oligonucleotide probes can be labeled with fluorescent labels and microbeads, with regard to instant claim 1.d reciting "detecting said optically distinguishable material in a sequential manner along said substantially linear hybridized DNA complex the recitation is interpreted as detecting one or more optically distinguishable DNA sequence recognition units in a sequential manner along a substantially linear hybridized DNA complex, which is taught by Bensimon.

Bensimon discloses a method for aligning macromolecules such as polymers or macromolecules with biological activity, especially DNA, or proteins and also relates to the application of this method in processes for detecting, for measuring intramolecular distance, for separating and/or for assaying a macromolecule in a sample. Macromolecules such as nucleic acids, proteins, lipids or polysaccharides are aligned on a support surface by passing the macromolecules through a meniscus of a solvent containing the macromolecules. The meniscus may be that of a solvent between two surfaces at an interface of the solvent with air. One end of a macromolecule is attached to one surface which may be a glass surface and another end is free. The meniscus is moved relative to the surface to which the end is attached such as by evaporating the solvent or by

moving the surface. As the macromolecule passes through the meniscus, the macromolecule aligns on the surface perpendicular to the meniscus. This method may be used in assaying, measuring intramolecular distance and/or separating of macromolecules.

The present invention relates to a method for single molecule identification of a target DNA molecule in a random coil state by attaching an optically distinguishable material to a DNA sequence recognition unit, which is specific to a particular sequence of DNA, hybridizing at least one optically distinguished DNA sequence recognition unit to a target DNA molecule in a random coil state, passing the target DNA molecule, now hybridized with at least one optically distinguished DNA sequence recognition unit, in a fluid carrier from a reservoir in a microfluidic device through a narrow channel to cause an acceleration of fluid flow through said channel, thereby causing the hybridized DNA complex to extend into a substantially linear configuration, d) detecting the optically distinguishable material in a sequential manner, determining, from this sequence of optically distinguished material, the sequential order of the specific DNA sequences of the target molecule to identify the target DNA molecule from its DNA sequence.

A claim is anticipated only if each and every element as set forth in the claim is found either expressly or inherently described in a single prior art reference. The identical invention must be shown in as complete detail as is contained in the claim. Claim 1.c reads "passing said hybridized DNA complex in a random coil state in a fluid carrier from a reservoir in a microfluidic device through a narrow channel to cause an acceleration of fluid flow through said channel, thereby causing said hybridized DNA complex to extend into a substantially linear configuration;" MPEP 2111.01 states that "the words of a claim must be given their "plain meaning" unless they are defined in the specification." This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989); Chef America, Inc. v. Lamb-Weston, Inc., 358 F.3d 1371, 1372, 69 USPQ2d 1857 (Fed. Cir. 2004) (Ordinary, simple English words whose meaning is clear and unquestionable, absent any indication that their use in a particular context changes their meaning, are construed to mean exactly what they say. Thus, "heating the

resulting batter-coated dough to a temperature in the range of about 400oF to 850oF" required heating the dough, rather than the air inside an oven, to the specified temperature.). Merriam-Webster Online Dictionary defines the term "through" to mean *"(1) -- used as a function word to indicate movement into at one side or point and out at another and especially the opposite side of <drove a nail through the board> (2): by way of <left through the door> (3) -- used as a function word to indicate passage from one end or boundary to another <a highway through the forest> <a road through the desert> (4): without stopping for: PAST <drove through a red light> b -- used as a function word to indicate passage into and out of a treatment, handling, or process <the matter has already passed through her hands>*". Cambridge on-line dictionaries define the term "through" to mean: *"from one end or side of something to the other, as in "They walked slowly through the woods." Or "We drove through the tunnel.""* The Compact Oxford English Dictionary defines "through" to mean: "1 moving in one side and out of the other side of (an opening or location)." Thus, the plain meaning of the term indicates that the hybridized DNA complex proceeds in one side of the channel and out the other. In addition, MPEP 2111.01 continues that ""Plain meaning" refers to the ordinary and customary meaning given to the term by those of ordinary skill in the art" and "It is the use of the words in the context of the written description and customarily by those skilled in the relevant art that accurately reflects both the "ordinary" and the "customary" meaning of the terms in the claims. Ferguson Beauregard/Logic Controls v. Mega Systems, 350 F.3d 1327, 1338, 69 USPQ2d 1001, 1009 (Fed. Cir. 2003) (Dictionary definitions were used to determine the ordinary and customary meaning of the words "normal" and "predetermine" to those skilled in the art. In construing claim terms, the general meanings gleaned from reference sources, such as dictionaries, must always be compared against the use of the terms in context, and the intrinsic record must always be consulted to identify which of the different possible dictionary meanings is most consistent with the use of the words by the inventor.)". The specification supports the definition of "through" as the movement of the hybridized DNA complex in one side of the channel and out the other side of the channel. See Fig. 1a and 1c (A, B, C, D, E, F). The Examiner also questions what part of the hybridized DNA complex passes through the channel. The plain wording of claim 1 indicates that the "hybridized DNA complex" passes through

the channel. Claim 1 does not say "part of the hybridized DNA complex" or "the hybridized DNA complex and any part thereof." The normal reading of the claim would indicate that the whole complex passes in one end and out the other. Fig. 1a and 1c also clarify what part of the complex passes through the channel. Fig. 1a (F) is located outside the exit of the narrow channel. Referring to Fig. 1c, it is clear from (F) that the whole molecule has passed through the channel.

OneLook® Dictionary at www.onelook.com defines the term "channel" to mean "a passage for water (or other fluids) to flow through" and "reservoir" to mean "tank used for collecting and storing a liquid (as water or oil)." According to MPEP 2111.01 as discussed above, these terms can be given their common meaning. This meaning is also supported by the specification. Figs. 1a and 1b make clear that the reservoir and channel are two separate parts of the microfluidic device. Review of Bensimon Fig. 6 indicates that there are not two separate and distinct parts of the device through which the hybridized complex passes.

The Examiner also indicates that Claim 1 does not recite any limitations with regard to how much of the DNA complex is passed through the channel and therefore movement of all but the fixed end of the DNA complex through the area between the plates as taught by Bensimon in Fig. 6 can be reasonably interpreted as passing the DNA complex through a narrow channel. As discussed above, the term "through" in claim 1 refers to movement of the hybridized DNA complex in one side and out the other of the channel. Bensimon makes no such disclosure. Also comparison of Fig. 6 of Bensimon to Fig 1a of the present invention would clearly indicate the difference between Bensimon and the present invention.

Therefore, as Bensimon fails to disclose the passage of a hybridized complex from a reservoir and in one side and out the other (through) a narrow channel, Bensimon fails to anticipate the present claims and Applicants request the Examiner to reconsider and withdraw the rejection.

Rejection of Claims 1-6 Under 35 U.S.C. §102(e):

The Examiner has rejected Claims 1-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Chan et al (hereinafter referred to as Chan-1; Pre Grant Publication 2003/0059822, 102(e) date 09/18/2001), as Chan-1 teaches a method of analyzing a polymer comprising labeling the polymer with first and

second unit specific makers, the first unit specific marker having a first label and the second unit specific marker including a second label distinct from the first label; exposing the labeled polymer to a detection station to produce distinct detection signals from the first and second labels; and identifying the distinct first and second signals, Chan-1 teaches that the first unit specific marker can be different than the second unit specific marker, either in its nature or in the polymer unit it recognizes and binds to, Chan-1 also teaches that the first unit specific marker can be identical to the second unit specific marker, yet the first and second unit specific markers are labeled with distinct labels, Chan-1 also teaches that the polymer is preferably a nucleic cid that is genomic DNA and that the unit specific marker can be a nucleic acid probe, or a peptide or polypeptide or peptide-nucleic acids, Chan-1 teaches that unit specific markers are attached to optically distinguishable labels that include a fluorescent molecule, a radioisotope, an enzyme, a biotin molecule, an avidin molecule, a semiconductor nanocrystal, a semiconductor nanoparticle, a colloid gold nanocrystal, a micro bead, a protein, a peptide, a nucleic acid, a carbohydrate, an antigen, an antibody, etc., Chan-1 teaches that the pattern of binding of the unit specific markers to the polymer may be determined using a variety of systems including a linear polymer analysis system, such as optical mapping or DNA combing, Chan-1 teaches that the unit specific marker (and thus the polymer) can be sequentially exposed to a station, "station" defined as a region where a portion of the polymer is exposed to an energy source in order to produce a signal or polymer dependent impulse, by movement of the marker and the station relative to one another, Chan-1 teaches that the polymer can be aligned and stretched before it reaches the interaction station and that a very effective technique of stretching DNA is to pass the polymer through a tapered microchannel having an obstacle field, followed by a constant-shear section to maintain the stretching obtained and straighten out any remaining coiling in the polymer. The Examiner indicates that, with regard to instant claim 1.d reciting "detecting said optically distinguishable material in a sequential manner along said substantially linear hybridized DNA complex" the recitation is interpreted as detecting one or more optically distinguishable DNA sequence recognition units in a sequential manner along a substantially linear hybridized DNA complex, which is taught by Chan-1.

Chan-1 provides methods and systems for improved spatial resolution of signal detection, particularly as applied to the analysis of polymers such as biological polymers. The methods and systems comprise differentially tagging polymers in order to increase resolution. The disclose method for analyzing a polymer comprises: a) providing a detection station having a known detection resolution; b) labeling the polymer with first and second unit specific markers, the first unit specific marker including a first label and the second unit specific marker including a second label distinct from the first label, wherein the first and second unit specific markers are spaced apart on the polymer such that, if the labels were not distinct from each other, they would be separated by a distance less than the detection resolution; c) exposing the polymer labeled as in (b) to the detection station to produce distinct first and second signals arising from the first and second labels; and d) identifying the distinct first and second signals.

The present invention relates to a method for single molecule identification of a target DNA molecule in a random coil state by attaching an optically distinguishable material to a DNA sequence recognition unit, which is specific to a particular sequence of DNA, hybridizing at least one optically distinguished DNA sequence recognition unit to a target DNA molecule in a random coil state, passing the target DNA molecule, now hybridized with at least one optically distinguished DNA sequence recognition unit, in a fluid carrier from a reservoir in a microfluidic device through a narrow channel to cause an acceleration of fluid flow through said channel, thereby causing the hybridized DNA complex to extend into a substantially linear configuration, d) detecting the optically distinguishable material in a sequential manner, determining, from this sequence of optically distinguished material, the sequential order of the specific DNA sequences of the target molecule to identify the target DNA molecule from its DNA sequence.

37 CFR 1.131 states "(a) When any claim of an application or a patent under reexamination is rejected, the inventor of the subject matter of the rejected claim, the owner of the patent under reexamination, or the party qualified under §§ 1.42, 1.43, or 1.47, may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based. The effective date of a U.S. patent, U.S. patent application

publication, or international application publication under PCT Article 21(2) is the earlier of its publication date or date that it is effective as a reference under 35 U.S.C. 102(e). Prior invention may not be established under this section in any country other than the United States, a NAFTA country, or a WTO member country. Prior invention may not be established under this section before December 8, 1993, in a NAFTA country other than the United States, or before January 1, 1996, in a WTO member country other than a NAFTA country."

Chan-1 was filed September 18, 2002, and has priority under 102(e) to September 18, 2001. Applicants conceived the present invention in the U.S. before the applicable 102(e) date of the applied reference, as shown in the attached 37 CFR 1.131 Declaration of co-inventor Zhihao Yang, Tiecheng A. Qiao, Susan J. Muller, and Dorian Liepmann, attached herewith. The invention was first recorded in the notebook of Mr. Yang on June 5, 2001 (European date notation), and was entered into a tracking database (Invention Tracker) and submitted to the legal department of Eastman Kodak Company for preparation of the currently pending patent application in August of 2001. Preparation of the application occurred between August 27, 2001, and the filing date of February 28, 2002, as previously submitted. As shown in the Declaration and documents attached thereto, Applicants date of conception pre-dates the applied references of Chan-1, the Applicants diligently pursued a constructive reduction to practice in the form of the currently pending patent application. Therefore, the Applicants request that the Examiner withdraw the rejection, as Chan-1 does not anticipate the present invention.

Rejection of Claims 1-8 Under 35 U.S.C. §102(e):

The Examiner has rejected Claims 1-8 under 35 U.S.C. 102(e) as being anticipated by Hannah et al (hereinafter referred to as Hannah; U.S. Patent 6,767,731 B2, 102(e) date 08/27/2001).

Hannah teaches a method of sequencing a target nucleic acid comprising hybridization of the target DNA with probes, which can be oligonucleotides and oligonucleotide analogs that are uniquely and detectably labeled, using a microfluidic device to pass the hybridized nucleic acid through a microchannel to extend it to an approximate linear conformation by hydrodynamic focusing, and detecting the spectral signature of each labeled

probe, preferably in sequential order (instant claims 1, 5 and 6; see column 2, lines 38-44 and 51-56, and column 3, lines 3-7 and 9-11 of Hannah). Hannah also teaches that nucleic acid molecules sequenced by this method can be DNA or RNA (instant claim 1; see column 4, lines 62-65 of Hannah). Hannah also teaches that the probes used for this method can be DNA, RNA, or analog thereof, such as a peptide nucleic acid (instant claims 5 and 6; see column 6, lines 30-34 of Hannah). Hannah also teaches that the probe labels can be fluorescent, luminescent, radioactive, phosphorescent, chemiluminescent, enzymatic, spin, electron dense, mass spectroscopic, semiconductor nanostructures, and quantum dots (instant claims 2-4; see column 8, lines 42-47 and column 10, lines 12-37 of Hannah). Hannah also teaches that photolithography can be used to obtain microchannels for use in linearizing DNA in the range of tens of micrometers wide and deep (instant claims 7-9; see column 12, lines 14-16 of Hannah). With regard to instant claim 1.d reciting "detecting said optically distinguishable material in a sequential manner along said substantially linear hybridized DNA complex,... ", the recitation is interpreted as detecting one or more optically distinguishable DNA sequence recognition units in a sequential manner along a substantially linear hybridized DNA complex, which is taught by Hannah (see column 2, lines 38-44 and 51-56, and column 3, lines 3-7 and 9-11 of Hannah).

Hannah relates to the fields of molecular biology and nucleic acid analysis. In particular, the invention relates to methods, composition and apparatus for electron-induced fluorescent DNA sequencing. Hannah provides an apparatus, compositions and related methods for sequencing a target nucleic acid. In certain embodiments, the apparatus is a microfluidic apparatus comprising an input chamber, microchannel, output chamber and a detection unit that is operatively connected to the microchannel. In preferred embodiments, the methods include hybridizing a target nucleic acid to one or more probe libraries, moving the hybridized target nucleic acid past the detector, and detecting bound probes. Probe libraries may comprise oligonucleotides or oligonucleotide analogs, preferably with each probe uniquely labeled. A linear order of labeled probes hybridized to the target nucleic acid can be detected and the target nucleic acid sequence deduced. In preferred embodiments, probe labels are detected by analysis of electron- induced fluorescence of probes labeled with conductive polymers.

The present invention relates to a method for single molecule identification of a target DNA molecule in a random coil state by attaching an optically distinguishable material to a DNA sequence recognition unit, which is specific to a particular sequence of DNA, hybridizing at least one optically distinguished DNA sequence recognition unit to a target DNA molecule in a random coil state, passing the target DNA molecule, now hybridized with at least one optically distinguished DNA sequence recognition unit, in a fluid carrier from a reservoir in a microfluidic device through a narrow channel to cause an acceleration of fluid flow through said channel, thereby causing the hybridized DNA complex to extend into a substantially linear configuration, d) detecting the optically distinguishable material in a sequential manner, determining, from this sequence of optically distinguished material, the sequential order of the specific DNA sequences of the target molecule to identify the target DNA molecule from its DNA sequence.

37 CFR 1.131 states "(a) When any claim of an application or a patent under reexamination is rejected, the inventor of the subject matter of the rejected claim, the owner of the patent under reexamination, or the party qualified under §§ 1.42, 1.43, or 1.47, may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based. The effective date of a U.S. patent, U.S. patent application publication, or international application publication under PCT Article 21(2) is the earlier of its publication date or date that it is effective as a reference under 35 U.S.C. 102(e). Prior invention may not be established under this section in any country other than the United States, a NAFTA country, or a WTO member country. Prior invention may not be established under this section before December 8, 1993, in a NAFTA country other than the United States, or before January 1, 1996, in a WTO member country other than a NAFTA country."

Hannah et al. was first filed in the United States August 27, 2001. Applicants conceived the present invention in the U.S. before the applicable 102(e) date of the applied reference, as shown in the attached 37 CFR 1.131 Declaration of co-inventor Zhihao Yang, Tiecheng A. Qiao, Susan J. Muller, and Dorian Liepmann, attached herewith. The invention was first recorded in the

notebook of Mr. Yang on June 5, 2001 (European date notation), and was entered into a tracking database (Invention Tracker) and submitted to the legal department of Eastman Kodak Company for preparation of the currently pending patent application in August of 2001. Preparation of the application occurred between August 27, 2001, and the filing date of February 28, 2002, as previously submitted. As shown in the Declaration and documents attached thereto, Applicants date of conception pre-dates the applied references of Hannah, the Applicants diligently pursued a constructive reduction to practice in the form of the currently pending patent application. Therefore, the Applicants request that the Examiner withdraw the rejection, as Hannah does not anticipate the present invention.

The previously submitted declaration provides "notebook page 154" which discloses the steps of: a) attaching different oligonucleotides with different colored beads, b) hybridizing the labeled oligonucleotides with unknown DNA molecule, c) stretching the DNA molecules from random coil to linear confirmation under microscopy by a microfluidic device as shown in Berkeley, d) and recording the order of colored beads to determine the species of DNA. "Berkley" refers to the article "Effect of Flow on Complex Biological Macromolecules in Microfluidic Devices", as indicated in the attached Declaration of co-inventor Zhihao Yang, Tiecheng A. Qiao, Susan J. Muller, and Dorian Liepmann. The article, included herewith, discloses a "reservoir" from which the DNA is passed, and teaches how the stretching of the DNA relates to the "acceleration of fluid flow through said channel" recited in instant claim 1.

Rejection Of Claims 1-8 Under 35 U.S.C. §103(a):

The Examiner has rejected Claims 1-8 under 35 U.S.C. §103(a) as being unpatentable over Bensimon, in view of Chan-2 (hereinafter referred to as Chan-2; PCT/US00/22253, International Publication Number WO 01 /13088 Al, International Publication Date 02/22/2001), indicating that, for the instant rejection, the recited phrase "from a reservoir in a microfluidic device " is interpreted as the hybridized DNA initially being in a separate chamber in a device having channels with dimensions in the micrometer range. In addition, passing the hybridized DNA complex through a "narrow channel to cause an acceleration of flow through said channel, thereby causing said hybridized DNA complex to extend into a substantially linear configuration;" is interpreted as the

entire hybridized DNA complex being passed through a narrow channel and extended to a linear configuration due to the hydrodynamic forces associated with the accelerated microfluidic flow of the fluid containing the hybridized DNA complex through the channel, Bensimon teaches a method of analyzing DNA comprising hybridizing the DNA in solution with probes having fluorescent reagents and then detecting the position of the probes after aligning, Bensimon also teaches that DNA molecules placed in a channel between cover slips can be aligned by the evaporation flow parallel to a moving meniscus in the channel, Bensimon also teaches that the probes used to hybridize to DNA can be oligonucleotides, RNA, DNA, and peptide nucleic acids, Bensimon also teaches that oligonucleotide probes can be labeled with fluorescent labels and microbeads, with regard to instant claim 1.d reciting "detecting said optically distinguishable material in a sequential manner along said substantially linear hybridized DNA complex,... ", the recitation is interpreted as detecting one or more optically distinguishable DNA sequence recognition units in a sequential manner along a substantially linear hybridized DNA complex, which is taught by Bensimon (see column 16, lines 50-55 of Bensimon). The Examiner indicates that, although Bensimon does not teach a method of linearizing a hybridized DNA complex by hydrodynamic force employing a microfluidic device, having dimensions in the micrometer range, to pass the entire hybridized DNA complex from a separate reservoir into a narrow channel, Chan-2 teaches that since microfluidic devices allow multiple molecules to be stretched in succession, extremely high throughput screening can be achieved, Chan-2 teaches that the method of linearizing DNA used by Bensimon, known as "molecular combing", cannot be easily adapted to a high-throughput operation because the immobilization of the polymers is a rate-limiting step and further modification of the polymers is more difficult after immobilization, Chan-2 also teaches that molecular combing and other polymer stretching techniques are lacking in the uniformity and reproducibility of stretching, ease of handling of the biopolymer, applicability to all types and sizes of biopolymers, and the ability to rapidly analyze information, Chan-2 also teaches detailed microfluidic polymer stretching structures, which enable stretching by hydrodynamic force, with various widths and depths and accompanying stretching methods, specifically, Chan-2 teaches that a channel with 1 .1m depth, 1 mm length, and a shear rate of 0.25/s gives a force of

approximately 0.25 pN, which the inventors have verified experimentally is adequate to stretch DNA, making it prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of linearizing DNA taught by Bensimon in the method of DNA analysis taught by Bensimon with the DNA linearizing method taught by Chan-2 because Chan-2 teaches that this method for linearizing DNA is capable of extremely high-throughput operation and allows rapid analysis on a reasonable timescale and the ordinary artisan would have been motivated to replace the method of linearizing DNA taught by Bensimon with the method of linearizing DNA taught by Chan-2 for the purpose of improving the method of Bensimon because Chan-2 teaches that molecular combing as taught Bensimon cannot be easily adapted to a high-throughput operation and is incapable of rapid analysis of information, while the method of Chan-2 is readily capable of extremely high-throughput operation and rapid analysis of information and, in addition, Chan-2 teaches specific examples of microfluidic structures for stretching DNA with their dimensions and the methods for fabrication of such structures.

Bensimon discloses a method for aligning macromolecules such as polymers or macromolecules with biological activity, especially DNA, or proteins and also relates to the application of this method in processes for detecting, for measuring intramolecular distance, for separating and/or for assaying a macromolecule in a sample. Macromolecules such as nucleic acids, proteins, lipids or polysaccharides are aligned on a support surface by passing the macromolecules through a meniscus of a solvent containing the macromolecules. The meniscus may be that of a solvent between two surfaces at an interface of the solvent with air. One end of a macromolecule is attached to one surface which may be a glass surface and another end is free. The meniscus is moved relative to the surface to which the end is attached such as by evaporating the solvent or by moving the surface. As the macromolecule passes through the meniscus, the macromolecule aligns on the surface perpendicular to the meniscus. This method may be used in assaying, measuring intramolecular distance and/or separating of macromolecules.

Chan-2 relates to the general field of polymer characterization. More particularly, the invention relates to the use of structures to stretch a polymer or to select a polymer on the basis of length in a chip. The invention

provides structures and methods that allow polymers of any length, including nucleic acids containing entire genomes, to be stretched into a long, linear conformation for further analysis. The invention also provides structures and methods for selecting and stretching polymers based on their lengths. Polymers are loaded into a device and run through the structures. Stretching is achieved by, e.g., applying shear forces as the polymer passes through the structures, placing obstacles in the path of the polymer, or a combination thereof. Since multiple molecules may be stretched in succession, extremely high throughput screening, e.g. , screening of more than one molecule per second, is achieved.

The present invention relates to a method for single molecule identification of a target DNA molecule in a random coil state by attaching an optically distinguishable material to a DNA sequence recognition unit, which is specific to a particular sequence of DNA, hybridizing at least one optically distinguished DNA sequence recognition unit to a target DNA molecule in a random coil state, passing the target DNA molecule, now hybridized with at least one optically distinguished DNA sequence recognition unit, in a fluid carrier from a reservoir in a microfluidic device through a narrow channel to cause an acceleration of fluid flow through said channel, thereby causing the hybridized DNA complex to extend into a substantially linear configuration, d) detecting the optically distinguishable material in a sequential manner, determining, from this sequence of optically distinguished material, the sequential order of the specific DNA sequences of the target molecule to identify the target DNA molecule from its DNA sequence.

To establish a prima facia case of obviousness, there must be some suggestion or motivation in the reference or in the general knowledge available to one skilled in the art to modify the reference, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all the claim limitations.

As discussed above, Claim 1.c reads "passing said hybridized DNA complex in a random coil state in a fluid carrier from a reservoir in a microfluidic device through a narrow channel to cause an acceleration of fluid flow through said channel, thereby causing said hybridized DNA complex to extend into a substantially linear configuration;" MPEP 2111.01 states that "the words of a claim must be given their "plain meaning" unless they are defined in

the specification." This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989); Chef America, Inc. v. Lamb-Weston, Inc., 358 F.3d 1371, 1372, 69 USPQ2d 1857 (Fed. Cir. 2004) (Ordinary, simple English words whose meaning is clear and unquestionable, absent any indication that their use in a particular context changes their meaning, are construed to mean exactly what they say. Thus, "heating the resulting batter-coated dough to a temperature in the range of about 400oF to 850oF" required heating the dough, rather than the air inside an oven, to the specified temperature.). Merriam-Webster Online Dictionary defines the term "through" to mean *"(1) -- used as a function word to indicate movement into at one side or point and out at another and especially the opposite side of <drove a nail through the board> (2): by way of <left through the door> (3) -- used as a function word to indicate passage from one end or boundary to another <a highway through the forest> <a road through the desert> (4): without stopping for: PAST <drove through a red light> b -- used as a function word to indicate passage into and out of a treatment, handling, or process <the matter has already passed through her hands>*". Cambridge on-line dictionaries define the term "through" to mean: *"from one end or side of something to the other, as in "They walked slowly through the woods." Or "We drove through the tunnel.""* The Compact Oxford English Dictionary defines "through" to mean: "1 moving in one side and out of the other side of (an opening or location)." Thus, the plain meaning of the term indicates that the hybridized DNA complex proceeds in one side of the channel and out the other. In addition, MPEP 2111.01 continues that ""Plain meaning" refers to the ordinary and customary meaning given to the term by those of ordinary skill in the art" and "It is the use of the words in the context of the written description and customarily by those skilled in the relevant art that accurately reflects both the "ordinary" and the "customary" meaning of the terms in the claims. Ferguson Beauregard/Logic Controls v. Mega Systems, 350 F.3d 1327, 1338, 69 USPQ2d 1001, 1009 (Fed. Cir. 2003) (Dictionary definitions were used to determine the ordinary and customary meaning of the words "normal" and "predetermine" to those skilled in the art. In construing claim terms, the general meanings gleaned from reference sources, such as dictionaries, must always be compared against the use of the terms in context, and the intrinsic record must

always be consulted to identify which of the different possible dictionary meanings is most consistent with the use of the words by the inventor.)". The specification supports the definition of "through" as the movement of the hybridized DNA complex in one side of the channel and out the other side of the channel. See Fig. 1a and 1c (A, B, C, D, E, F). The Examiner also questions what part of the hybridized DNA complex passes through the channel. The plain wording of claim 1 indicates that the "hybridized DNA complex" passes through the channel. Claim 1 does not say "part of the hybridized DNA complex" or "the hybridized DNA complex and any part thereof." The normal reading of the claim would indicate that the whole complex passes in one end and out the other. Fig. 1a and 1c also clarify what part of the complex passes through the channel. Fig. 1a (F) is located outside the exit of the narrow channel. Referring to Fig. 1c, it is clear from (F) that the whole molecule has passed through the channel. In addition, OneLook® Dictionary at www.onelook.com defines the term "channel" to mean "a passage for water (or other fluids) to flow through" and "reservoir" to mean "tank used for collecting and storing a liquid (as water or oil)." According to MPEP 2111.01 as discussed above, these terms can be given their common meaning. This meaning is also supported by the specification. Figs. 1a and 1b make clear that the reservoir and channel are two separate parts of the microfluidic device. Review of Bensimon Fig. 6 indicates that there are not two separate and distinct parts of the device through which the hybridized complex passes.

Neither Bensimon et al. nor Chan-2 disclose or suggest passing a hybridized DNA complex as presently claimed from a reservoir in a microfluidic device through a channel to sequence the target DNA molecule, thereby allowing identification of the target molecule. Since neither reference discloses passing a hybridized DNA complex as presently claimed from a reservoir in a microfluidic device through a channel, the combined references fail to provide a likelihood of success that one would be able to sequence the target DNA molecule, thereby allowing identification of the target molecule. Since neither Bensimon et al. nor Chan-2 disclose or suggest passing a hybridized DNA complex as presently claimed from a reservoir in a microfluidic device through a channel to sequence the target DNA molecule, thereby allowing identification of the target molecule, the references fail to disclose all the present claim limitations. Therefore, since

the combination of the references fail to produce the presently claimed invention, fail to provide any likelihood of success and fail to disclose all the present claims limitations, the Applicants request that the Examiner reconsider and withdraw the rejection.

Rejection Of Claims 7 and 8 Under 35 U.S.C. §103(a):

The Examiner has rejected Claims 7 and 8 under 35 U.S.C. 103(a) as being unpatentable over Chan-1, in view of Chan et al (hereinafter referred to as Chan-2; PCT/USOO/22253, International Publication Number WO 01 /13088 Al, International Publication Date 02/22/2001), as Chan-1 teaches a method of analyzing a polymer comprising labeling the polymer with first and second unit specific makers, the first unit specific marker having a first label and the second unit specific marker including a second label distinct from the first label; exposing the labeled polymer to a detection station to produce distinct detection signals from the first and second labels; and identifying the distinct first and second signals, Chan-1 also teaches that the first unit specific marker can be different than the second unit specific marker, either in its nature or in the polymer unit it recognizes and binds to, Chan-1 also teaches that the first unit specific marker can be identical to the second unit specific marker, yet the first and second unit specific markers are labeled with distinct labels, Chan-1 also teaches that the polymer is preferably a nucleic acid that is genomic DNA, and that the unit specific marker can be a nucleic acid probe, Chan-1 teaches that unit specific markers are attached to optically distinguishable labels that include a fluorescent molecule, a radioisotope, an enzyme, a biotin molecule, an avidin molecule, a semiconductor nanocrystal, a semiconductor nanoparticle, a colloid gold nanocrystal, a micro bead, a protein, a peptide, a nucleic acid, a carbohydrate, an antigen, an antibody, etc., Chan-1 teaches that the pattern of binding of the unit specific markers to the polymer may be determined using a variety of systems including a linear polymer analysis system, Chan-1 teaches that the unit specific marker (and thus the polymer) can be sequentially exposed to a station, "station" defined as a region where a portion of the polymer is exposed to an energy source in order to produce a signal or polymer dependent impulse, by movement of the marker and the station relative to one another, Chan-1 teaches that the polymer can be aligned and stretched before it reaches the interaction station and that a very effective technique of stretching DNA is to pass the polymer through a

tapered microchannel having an obstacle field, followed by a constant-shear section to maintain the stretching obtained and straighten out any remaining coiling in the polymer, Chan-1 teaches that pressure flow is the preferred driving force of the DNA through such a microchannel recited above (see page 14, para 0128 of Chan-1), with regard to instant claim 1.d) reciting "detecting said optically distinguishable material in a sequential manner along said substantially linear hybridized DNA complex, ...", the recitation is interpreted as detecting one or more optically distinguishable DNA sequence recognition units in a sequential manner along a substantially linear hybridized DNA complex, which is taught by Chan-1, and Chan-1 teaches stretching DNA by passing the DNA through a microchannel. The Examiner continues that, although Chan-1 is silent with respect to the width or depth of the channel, Chan-2 teaches that a channel with 1 μm depth, 1 mm length, and a shear rate of 0.25/s gives a force of approximately 0.25 pN, which the inventors have verified experimentally is adequate to stretch DNA, making it prima facie obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Chan-1 with the device of Chan-2 because Chan-2 specifically teaches a device for performing the method of Chan-1 and the ordinary artisan would have been motivated to use the device of Chan-2 because Chan-1, while generally teaching a method of stretching DNA with a microfluidic device, is silent with regard to the specific structure and dimensions of the device, the device, with its specific dimensions, taught by Chan-2 functions to stretch DNA as taught by Chan-1, the ordinary artisan would be motivated to use the device of Chan-2 in the method of Chan1 because Chan-1 teaches to stretch DNA by passing the DNA through a microchannel, but no specific structure or dimensions of the microchannel are recited.

Chan-1 provides methods and systems for improved spatial resolution of signal detection, particularly as applied to the analysis of polymers such as biological polymers. The methods and systems comprise differentially tagging polymers in order to increase resolution. The disclose method for analyzing a polymer comprises: a) providing a detection station having a known detection resolution; b) labeling the polymer with first and second unit specific markers, the first unit specific marker including a first label and the second unit specific marker including a second label distinct from the first label, wherein the first and second unit specific markers are spaced apart on the polymer such that, if

the labels were not distinct from each other, they would be separated by a distance less than the detection resolution; c) exposing the polymer labeled as in (b) to the detection station to produce distinct first and second signals arising from the first and second labels; and d) identifying the distinct first and second signals.

Chan-2 relates to the general field of polymer characterization. More particularly, the invention relates to the use of structures to stretch a polymer or to select a polymer on the basis of length in a chip. The invention provides structures and methods that allow polymers of any length, including nucleic acids containing entire genomes, to be stretched into a long, linear conformation for further analysis. The invention also provides structures and methods for selecting and stretching polymers based on their lengths. Polymers are loaded into a device and run through the structures. Stretching is achieved by, e.g., applying shear forces as the polymer passes through the structures, placing obstacles in the path of the polymer, or a combination thereof. Since multiple molecules may be stretched in succession, extremely high throughput screening, e.g. , screening of more than one molecule per second, is achieved.

The present invention relates to a method for single molecule identification of a target DNA molecule in a random coil state by attaching an optically distinguishable material to a DNA sequence recognition unit, which is specific to a particular sequence of DNA, hybridizing at least one optically distinguished DNA sequence recognition unit to a target DNA molecule in a random coil state, passing the target DNA molecule, now hybridized with at least one optically distinguished DNA sequence recognition unit, in a fluid carrier from a reservoir in a microfluidic device through a narrow channel to cause an acceleration of fluid flow through said channel, thereby causing the hybridized DNA complex to extend into a substantially linear configuration, d) detecting the optically distinguishable material in a sequential manner, determining, from this sequence of optically distinguished material, the sequential order of the specific DNA sequences of the target molecule to identify the target DNA molecule from its DNA sequence.

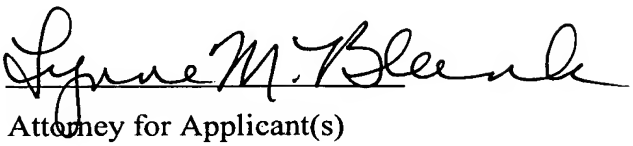
37 CFR 1.131 states "(a) When any claim of an application or a patent under reexamination is rejected, the inventor of the subject matter of the rejected claim, the owner of the patent under reexamination, or the party qualified under §§ 1.42, 1.43, or 1.47, may submit an appropriate oath or

declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based. The effective date of a U.S. patent, U.S. patent application publication, or international application publication under PCT Article 21(2) is the earlier of its publication date or date that it is effective as a reference under 35 U.S.C. 102(e). Prior invention may not be established under this section in any country other than the United States, a NAFTA country, or a WTO member country. Prior invention may not be established under this section before December 8, 1993, in a NAFTA country other than the United States, or before January 1, 1996, in a WTO member country other than a NAFTA country."

As discussed above, Chan-1 was filed September 18, 2002, and has priority under 102(e) to September 18, 2001. As shown in the present Declaration, as well as the previous Declaration of Yang and documents attached thereto, Applicants date of conception pre-dates the applied references of Chan-1, and Applicants diligently pursued a constructive reduction to practice in the form of the currently pending patent application, removing Chan-1 as a reference. Chan-2 does not teach or suggest all the features of the claimed invention. Therefore, the Applicants request that the Examiner reconsider and withdraw the rejection.

It is believed that the foregoing is a complete response to the Office Action and that the claims are in condition for allowance. Favorable reconsideration and early passage to issue is therefore earnestly solicited.

Respectfully submitted,



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